The effects of the sympathetic nerves on lumbar radicular pain: a behavioural and immunohistochemical study.

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The 'Discussion' section of this important paper highlights the findings from recent studies that sympathetic afferents are now known to play a major part in the transmission of pain impulses arising from the lumbar annulus fibrosus, posterior longitudinal ligament and adjacent structures. These afferent fibres ascend through the paravertebral sympathetic trunk to enter the somato-sensory tracts via the white rami communicantes at the L1, L2 levels. This is part of a dual sensory system, the other sensory fibres passing segmentally through the adjacent dorsal root ganglia. The afferent endings of this sympathetic supply have the potential to be peripherally sensitised through the activity of adjacent post-ganglionic sympathetic efferent endings and this pattern is similar to that found in enteric structures. Hence these spinal structures have been described as having in part a 'visceral pain' supply.

The experimental technique involved ligatures firmly tied around the left L5 nerve roots just proximal to the dorsal root ganglion (DRG) in two cohorts of rats matched with controls and sham groups. The sensitivity of the hindfoot to mechanical and heat stimuli, as judged by the withdrawal response, was recorded in the first cohort as above and then in the second cohort, who in addition to the left L5 root ligations had undergone an L2-L5 sympathectomy. The first cohort (the non-sympathectomy group) developed a significantly enhanced withdrawal response in their left hindlimbs over ten days following surgery, compared with their right hindlimbs and this response was significantly attenuated in the second or sympathectomy cohort. Random sections through the L5 and L4 DRGs were examined histologically after 28 days. Tyrosine hydroxylase immuno-reactive (THIR) staining was used to identify sympathetic efferent fibres and their endings. These were found to be significantly more numerous in the ipsilateral left L5 and also L4 DRG sections compared with the contralateral DRG specimens using a counting grid system. Presumably these histological changes developed during the first ten days following surgery and, as such, coincided with the development of the hypersensitivity in the affected hindfoot, though it is a pity that earlier DRG specimens from rats killed at one and two weeks in order to monitor the sympathetic efferent proliferation were not undertaken.

It is assumed that the left L5 root ligature was tightened to the point of creating total motor and sensory paralysis in that root (ie the equivalent of a nerve root ablation), albeit just proximal to the DRG. On this basis it must be assumed that the enhanced hypersensitivity of the hindfoot was mediated through the adjacent nerve roots. Certainly this was confirmed at L4. Presumably S1 would have been similarly affected and one wonders how far the segmental pattern of sympathetic sprouting in the DRGs had spread. In this respect, it is a criticism that more DRGs particularly at L3 and S1 were not sectioned on the ipsilateral left side, a relatively straightforward addition to the post mortem procedure.

One of the interesting challenges that this current experimental model raises is the means by which each 'sensitised' DRG sensory neurone completes the reflex cycle to reproduce the exaggerated hind foot withdrawal response. Clearly with the L5 nerve root ablated just proximal to the DRG, the reflex cycle must take another route. The authors reasonably suggest that with sympathetic efferent sprouting apparent also in the adjacent DRGs (as discussed, they only examined L4) that the reflex cycle producing this exaggerated response was indeed mediated via the hypersensitive L4 DRG and probably more widely along intact sensory nerves and also with the reflex synapses extending up and down the grey matter in the lumbar spinal cord.

An even more searching question concerns the mechanism by which an 'uninjured' DRG produces sympathetic efferent sprouting. The authors suggest that this neuro-hormonal process occurs via the paravertebral sympathetic chain through the secretion of neuropeptides such as nerve growth factor (NGF) among other neuronal growth stimulants and references are cited in support of this. If one is going to be critical of any area of this study it must be that no TH-IR histological studies were made on ipsilateral left DRGs following sympathectomy. If the adjacent DRGs in these rats had shown no histological evidence of sympathetic efferent sprouting then the authors would have proved their case about this mechanism, whereas at the
moment it continues to remain hypothesis only, waiting for someone to pick up the batten of this experimental challenge.

Yet another area of interest is the difference in the DRG histology using TH-IR staining seen when experimental injury is further distal to the peripheral nerve, which has been previously described and referred to by the authors, compared with the findings of the present study. Why in the former study were the sympathetic endings observed to be enveloping the actual neurone cell in a basket like fashion, (presumably the actual cell body is what the authors meant by their term ‘soma’) as opposed to the sprouting which surrounded only the myelinated axons in the present observation. It is tempting to consider whether this has anything to do with the DRG response to axonal injury where the site of damage is so close to the ganglion. Against this is the authors observation that similar findings occurred in the ipsilateral L4 DRGs whose neurones were without injury. Again further work is needed to establish whether sympathetic efferent nerve proliferation is the main process affecting the DRG sensory neurones or whether this is all part of a larger complex mechanism involving other supporting or satellite cells within the DRG.

In conclusion the outcome of this pivotal study is likely to be two fold. One, practical, to define by properly controlled clinical studies the extent to which lumbar sympathetic block or indeed chemical sympathectomy can relieve acute and/or chronic radicular pain. The much cited study which demonstrates relief by a local anaesthetic block to the L2 ganglion of the sympathetic chain can only be regarded as an uncontrolled and very subjective report and needs to be repeated as a more controlled study. The other outcome is experimental, namely the need for further work of the kind described in this paper using not only ablation of nerves and their roots at different points to note the effects on the DRGs but also to study the response from irritant substances including discogenic nuclear material in the region of the dorsal root ganglion. This has already been studied experimentally on the roots of the cauda equine.

No doubt ‘sensitisation’ of the dorsal root ganglion sensory neurones is a complex process alongside the whole question of ‘peripheral sensitisation’ involving also the so-called ‘visceral pain’ concept.

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References